SUSTAINED RELEASE CAPSULE

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Abstract of **JP11049668**

PROBLEM TO BE SOLVED: To provide the subject capsule designed to gradually release physiologically active substances at sites ranging from the small to large intestines while preventing them from being decomposed or deactivated in the stomach to afford effective biological availability of the physiologically active substances.

SOLUTION: This sustained release capsule is obtained by uniformly coating the outer surface of a gelatin-predominant hard capsule encapsulated with physiologically active substances with a film material consisting of a natural polystccharide/polyhydric alcohol composition prepared by homogeneously kneading at least one kind of natural polysaccharide selected from carrageenan, alginic acid, alginate, alginic acid derivative, agar, locust bean gum, gum guaiac, pectin, xanthan gum, glucomannan, chitinous substance and pullulan, in a system of at least one kind selected from polyhydric alcohol, sugar alcohol, monosaccharide, disaccharide, trisaccharide and oligosaccharide.

[JP,11-049668,A]

CLAIMS

[Claim(s)]
[Claim 1] In at least one sort of systems chosen from polyhydric alcohol, sugar-alcohol, monosaccharide, disaccharide, trisaccharide, and an oligosaccharide A carrageenan, an alginic acid, alginate, an alginic-acid derivative, an agar, Locust bean gum, guar gum, an amylopectin, pectin, xanthan gum, At least one sort of natural polysaccharide chosen from glucomannan, the chitinous substance, and the pullulan for the film material which consists of natural polysaccharide and a polyhydric-alcohol constituent which kneaded to homogeneity and was obtained The sustained release capsule characterized by covering equally the outside surface of the hard capsule which uses gelatin as a principal component.
[Claim 2] The sustained release capsule according to claim 1 characterized by a fats-and-oils layer with a melting point of 40 degrees C or more intervening between the outside surfaces of a hard capsule and the layers of natural polysaccharide and a polyhydric-alcohol constituent which use gelatin as a principal component.
[Claim 3] The sustained release capsule according to claim 1 characterized by a fats-and-oils layer with a melting point of 40 degrees C or more existing in the outside surface of natural polysaccharide and a polyhydric-alcohol constituent.
[Claim 4] Claim 1 characterized by being covered with the coat which the front face covered with the film material which consists of natural polysaccharide and a polyhydric-alcohol constituent becomes from protein further thru/or a sustained release capsule given in three.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] This invention prevents the decomposition and deactivation in the stomach, and relates to the sustained release capsule to which a physiological active substance is made to emit gradually in the part from a small intestine to the large intestine.
[0002]
[Description of the Prior Art] When medicating the body with a physiological active substance conventionally, means, such as internal use, anus administration, and injection, are adopted. For internal use, a capsule, a tablet, a granule, liquids and solutions, powder, etc. are used. However, by the time the matter prescribed for the patient in taking orally resulted in the small intestine, it tended to be set in the stomach, and it tended to be disassembled or deactivated in response to the operation of strong acid and an enzyme.
[0003] The stomach is an organ which digests the food taken in. The carbohydrate in food is disassembled into a glucose through a dextrin, an oligosaccharide, and a maltose. Protein is disassembled into amino acid through a polypeptide. A fat is disassembled into a glycerol and a fatty acid. Although all the above-mentioned decomposition reactions are not performed in the stomach, physical, chemical [stomach], and stomach enzyme-disintegration are intense, and make food the shape of rice porridge of a half-fluidity. Consequently, digestion in the duodenum and digestion in a small intestine are performed easily. Especially the physical disintegration by stomach peristalsis and the chemical disintegration by strong hydrochloric-acid acidity are quite intense un-alternatively.
[0004] For the physiological active substance with which many were administered orally, this un-alternative and physicochemical disintegration are a negative factor. That is, it is decomposed in the stomach, and many drugs and physiological active substances deactivate, and are made to decrease effect sharply. Furthermore, the digested matter is absorbed in a small intestine. The physiological active substance administered orally is also digested with the stomach, and it is carried by the small intestine by high concentration, and is promptly absorbed by the small intestine, and blood drug concentration rises rapidly. However, even if it results in a small intestine according to the purpose of a physiological active substance, it is desirable to adjust the emission rate from a capsule. That is, the drug which carries out a direct action to the large intestine like the chemotherapic drug to colon cancer is made to reach the large intestine, without making almost absorb in a small intestine, and the physiological active substance with the prompt desirable absorption in a small intestine is adjusted so that it may be promptly emitted in a small intestine.
[0005] A physiological active substance is enclosed with the hard capsule which consists of gelatin, and the technique which covers an envelope with the special protein of the digestive resistance by stomach juice is also proposed. The capsule was digested within the stomach also by this technique. In JP,3-232815,A, these people manufactured the capsule which drilled much punching using the viscous solution obtained by dissolving natural polysaccharide and a polyhydric-alcohol constituent in water, enclosed with this capsule the physiological active substance which acts on intestines, and indicated the technique which covers this coat with edible hardened-oil fat with a melting point of 35

degrees C or more.
[0006]
[Problem(s) to be Solved by the Invention] However, when there was an inclination which it runs short of rigidity although the coat which consists of natural polysaccharide and a polyhydric-alcohol constituent has flexibility, and is physically damaged by gastroenteric intense peristalsis, industrial production was very difficult for the capsule which drilled much punching. Then, the physiological active substance [the physiological active substance] to make it acting effectively in the large intestine from a small intestine was administered orally, and the safeguard of a physiological active substance which reduction of the effect is prevented [safeguard] as much as possible in the stomach, and passes the stomach safely was called for. That is, with the stomach, it was hard to dissolve and the capsule which a physiological active substance emits gradually in the process in which the large intestine is passed from a small intestine was called for.
[0007]
[Means for Solving the Problem] This invention in at least one sort of systems chosen from polyhydric alcohol, sugar-alcohol, monosaccharide, disaccharide, trisaccharide, and an oligosaccharide A carrageenan, an alginic acid, alginate, an alginic-acid derivative, an agar, Locust bean gum, guar gum, pectin, an amylopectin, xanthan gum, At least one sort of natural polysaccharide chosen from glucomannan, the chitinous substance, and the pullulan for the film material which consists of natural polysaccharide and a polyhydric-alcohol constituent which kneaded to homogeneity and was obtained The outside surface of the hard capsule which uses as a principal component the gelatin with which the physiological active substance was enclosed covers equally. Most physiological active substances in a capsule remain in the capsule after stomach passage, and residual [the great portion of] is the capsule gradually emitted in the large intestine from a small intestine.
[0008] That is, this invention manufactures a sustained release capsule by covering equally the film material which becomes the outside surface of the hard capsule which uses existing gelatin as a principal component from natural polysaccharide and a polyhydric-alcohol constituent. In the alimentary canal of the body, the enzyme which digests naturally-ocurring-polymers polysaccharide does not exist. Furthermore, since the natural polysaccharide of this invention and the film material which consists of a polyhydric-alcohol constituent have semipermeability, it can become possible to make the physiological active substance contained in the capsule emit gradually by decomposition or the part from a small intestine to [without carrying out deactivation] the large intestine, and it can make a physiological active substance act on the part of the arbitration of the large intestine from a small intestine very effectively.
[0009]
[Embodiment of the Invention] The physiological active substance in this invention is matter which begins the food or drugs which acts on a living body useful, and has the bioactive of a wide sense. Drugs effective in diseases of varieties, such as an internal secretion metabolic error disease which makes representation the malignant tumor which makes representation cardiovascular disease, such as a heart blood vessel and blood pressure, pulmonary problems, a digestive system disease, and cancer, and diabetes mellitus as what is classified into drugs, are applicable. In addition, as a physiological

active substance of a wide sense, there is neurotransmitter, such as hormone Mr. matter, such as various kinds of hormone, such as pituitary hormone, an insulin, glucagon, Melatonin, and cytokinin, and prostaglandin, KAROPEPUCHIDO, and a kinin, a catecholamine, indoleamine, and acetylcholine, as matter of the marine organism origin which exists, for example in a nature. Moreover, supplements, such as useful bacteria in intestines, such as lactobacillus bifidus besides various vitamins and a mineral and lactic acid bacteria, royal jelly, a ginseng radix, the Quito acid, Nan Pao, a taurine, lecithin, flavonoid, chlorella, a fermented-soybeans kinase, and chondroitin, are mentioned.

[0010] With natural polysaccharide and a polyhydric-alcohol constituent, it is obtained by kneading to homogeneity at least one sort of natural polysaccharide chosen from a carrageenan, an alginic acid, alginate, an alginic-acid derivative, an agar, locust bean gum, guar gum, pectin, an amylopectin, xanthan gum, glucomannan, the chitinous substance, and the pullulan in at least one sort of systems chosen from the polyhydric alcohol, the sugar-alcohol, the monosaccharide, the disaccharide, the trisaccharide, and the oligosaccharide of narrow senses, such as a glycerol, ethylene glycol, propylene glycol, and diglycerol, the inside of the system of polyhydric alcohol -- **** -- when liquefied, in the solid case as it is or as 70% or more of a thick solution, it can be preferably used as 70 - 90% of a water solution 65 to 95%. A viscous water solution is obtained by adjusting the above-mentioned natural polysaccharide and polyhydric-alcohol constituent to predetermined water-solution concentration, and warming it. Moreover, covering film reinforcement can be raised by adding alkali at the time of adjustment.

[0011] A hard capsule can use the capsule which is the product made from gelatin usually marketed, or has the firmness which uses gelatin as a principal component. The sustained release capsule by this invention is obtained by making a solution with the above-mentioned viscous natural polysaccharide and polyhydric-alcohol constituent adhere, and making it dry, after enclosing the physiological active substance of the specified quantity with this hard capsule. In making a solution with viscous natural polysaccharide and polyhydric-alcohol constituent adhere, the means of immersion, spreading, and others can be used. although the amount of the natural polysaccharide and the polyhydric-alcohol constituent given to the outside surface of a hard capsule changes with the class of capsule, or classes of contents physiological active substance -- general -- the gelatin 100 weight section -- receiving -- natural polysaccharide and the polyhydric-alcohol constituent 50 - the 1000 weight sections -- it is the 100 - 500 weight section preferably.

[0012] It precedes covering natural polysaccharide and a polyhydric-alcohol constituent to a gelatine capsule, and if the thin coat of fats and oils with a melting point [like hardened oil] of 40 degrees C or more is formed in the outside surface of a gelatine capsule, the emission and deactivation of contents in the stomach will be controlled further. In order to form the thin coat of hardened oil, an emulsifier, water, or lower alcohol solutions, such as lecithin, etc. can be added and emulsified in fats and oils, it can cover with approaches, such as spreading and spray injection, to a hard capsule, and a solvent can be dried, or it can also be directly immersed in fats and oils. Or it is also effective to prepare a fats-and-oils layer in the outside of the layer of natural polysaccharide and a polyhydric-alcohol constituent.

[0013] It is also possible to prepare and protect the coat of still more nearly special protein to the outside surface of a capsule which has the coat of natural polysaccharide

and a polyhydric-alcohol constituent depending on the case. As special protein, the wheat protein containing many corn protein and gluten etc. can be mentioned. The digestive resistance in the stomach of a capsule not only improves, but the surface treatment effectiveness raises commodity value by preparing a proteinic coat.

[0014] Although some irregularity of the front face of a capsule does not interfere, it means [vocabulary / in this invention / "it covers equally"] that neither punching nor a crack part exists. Since it uses the permeability of a material from the purpose which makes internal gelatin digest gradually with digestive juices, such as stomach juice and pancreatic juice, since the coat of natural polysaccharide and a polyhydric-alcohol constituent causes the prompt elution of contents, it is not desirable. [of existence of punching, a crack part, etc.]

[0015] It has semipermeability, although the natural polysaccharide and the polyhydric-alcohol constituent of this invention are not digested. In the stomach, natural polysaccharide and a polyhydric-alcohol constituent are swollen under sufficient moisture existence, stomach juice is conjointly passed with the semipermeability, and stomach juice and the gelatin of a capsule contact. Consequently, the layer of natural polysaccharide and a polyhydric-alcohol constituent is thin, or when not precise enough, gelatin is digested in the stomach and contents are emitted. It does not only pass over the hard capsule made from gelatin to the base material of natural polysaccharide and a polyhydric-alcohol constituent, but a physiological active substance is emitted outside from natural polysaccharide and a polyhydric-alcohol constituent layer in the process in which the stomach and intestines are passed, and, finally the capsule material has become the piece of a coat crushed thinly.

[0016]

[Example]

Manufacture carrageenan of the covering liquid which consists of 2(1) natural polysaccharide, and [examples 1-2 and the example 1 of a comparison -] a polyhydric-alcohol constituent 60 weight sections glucomannan 20 weight sections guar gum Ten weight sections alginic acid Ten weight sections It mixed equally, and when the glycerol 30 weight section was added and having been kneaded at the room temperature (20 degrees C **10 degrees C), the natural polysaccharide and the polyhydric-alcohol constituent of the powder which has moisture mind somewhat were obtained. This constituent 3 weight section was dissolved in the water of 97 weight sections, and the viscous water solution was obtained.

[0017] (2) A water solution with viscous natural polysaccharide and polyhydric-alcohol constituent obtained by (1) is covered to the capsule made from gelatin which enclosed the manufacture lactobacillus bifidus of a sustained release capsule, it was dried, and this invention sustained release capsule was obtained. The capsule made from Warner Laon Byrd No. No. 1 gelatin was used for the capsule made from gelatin. 0.6**0.05g per capsule of lactobacillus bifidus was enclosed using the Amano Pharmaceuticals company make and BIFIZUSU "100" RONGAMU (number-of-micro-organisms 200x108 an individual/g). If it hit covering, natural polysaccharide and 130g of polyhydric-alcohol constituents per gelatin 100g were covered using full automatic film coating equipment (the product made from Freund, new high coating machine HCT-48N). (One example) Corn protein was covered with the rate of 30g per gelatin 100g on the front face of one example, and was made into two examples on it.

[0018] (3) Elution test liquid (enzyme addition) elution test liquid is a stomach internal secretion digestive enzyme pepsin (the Wako Pure Chem make and pepsin 1:10,000) to the 1st liquid, in order for the 1st liquid to make the 2nd stomach liquid approximate to intestinal pH according to a Japanese station, the 13th amendment, and General Test Procedures 159-162, respectively and to make the condition in the still more nearly actual stomach and intestines resemble. It added.
The 1st liquid .... NaCl .. 2.0g Dark HCl .. 7.0ml Pepsin .. Water was added to 1.0g and the whole quantity was set to 1000ml. The 2nd liquid uses the artificial intestinal juice formula of a "pharmaceutical-sciences great dictionary" (Japanese technology league), and is pancreatin (the Wako Pure Chem make, pancreatin). It added. Namely, the 2nd liquid .... Pancreatin .. 2.8g Water was added to 3..15.0g of NaHCO(s), and the whole quantity was set to 1000ml.
[0019] (4) The beaker which poured in the 100ml of the 1st liquid of the elution **** approach was placed during the hot bath of 37**2 degrees C of bath temperature, ten capsules manufactured by (2) to this beaker were put in, and shaking was continued for 2 hours (residence time in the general stomach). The beaker which poured in the 400ml of the 2nd liquid was placed during the hot bath of 37**2 degrees C of bath temperature, five capsules after a trial were put into this beaker with the 1st liquid, and shaking was continued for 16 hours (2 hours was deducted from 18 hours which is the residence time in an average alimentary canal of food).
[0020] (5) When weighing capacity of the dry weight of a capsule 16 hours [after test termination with the 1st liquid of test-result elution test liquid and with the 2nd liquid] after total elution time amount was carried out and the survival rate was computed, the example 1 and the example 2 were 92 - 94 % of the weight after the 1st liquid elution test, and the example 1 and the example 2 were 12 - 15 % of the weight after the 2nd liquid elution test.
[0021] As an example 1 of a comparison, except covering nothing on the surface of a gelatine capsule, the same capsule containing lactobacillus bifidus as the example 1 of this invention is used, and it is an example 2 of a comparison, It replaced with natural polysaccharide and a polyhydric-alcohol constituent, and other than having covered the equivalent mixture of corn protein and wheat protein with the rate of 70g per gelatin 100g, when the same trial was performed using the same capsule containing lactobacillus bifidus as the example 1 of this invention, the example 1 of a comparison and the example 2 of a comparison were immediately dissolved with the 1st liquid, and the wreckage of a capsule was not stopped. Weighing capacity of the capsule contents 18 hours [8 hours / with the 2nd liquid / (2 hour +6 hours) after total elution time amount and with the 2nd liquid] (2-hour +16 hours) after total elution time amount was carried out after test termination with the 1st liquid of elution test liquid, the survival rate was computed, and it was shown in Table 1. It is understood that this invention capsule has the large resistance over stomach juice, and the resistance over intestinal juice is also large.
[0022]
[Table 1]

[0023] An example 3 and manufacture carrageenan of an example 4 (1) sustained release capsule 20 weight sections glucomannan 30 weight sections pullulan 20 weight sections alginic acid 20 weight sections guar gum Ten weight sections The sustained release capsule of an example 3 entering lactobacillus bifidus was obtained like the example 1 except having used. The average weight of the gelatin per this capsule was [0.188g and the thickness of the average weight of 0.079g, and a natural polysaccharide and a polyhydric-alcohol constituent] about 400 micrometers. Moreover, after covering a capsule front face with the coat of hardened oil as an example 4, the sustained release capsule of entering [which was covered with natural polysaccharide and a polyhydric-alcohol constituent like the example 3] lactobacillus bifidus was obtained. Moisture was dried, after emulsifying hardened-oil MR-60 (the Miyoshi Oil & Fat Co., Ltd. make, melting point of 60 degrees C), using lecithin as hardened oil and spraying by the spray. The thickness of a fats-and-oils layer was presumed to be 50-70 micrometers. The number of bacilli of lactobacillus bifidus was measured about the capsule of an example 3 and an example 4. In the case of the 1st liquid, the number of micro organisms in a capsule was measured 2 hours after. In the case of the 2nd liquid, the number of micro organisms eluted in shaking liquid was measured.

[0024] (2) The measuring method culture medium of the number of micro organisms was

measured made in BEKUTON Dickinson and using gas pack 150TM using BL agar medium (EIKEN CHEMICAL CO., LTD. make).
[0025] (3) The number of micro organisms in the capsule after the trial of 2 hours with the 1st liquid of a test result was measured. Furthermore, it examined by having moved one capsule to the 2nd liquid, and the number of micro organisms emitted into the elution test liquid 6 hours (2-hour +4 hours) after total test time and of 18 hours (2-hour +16 hours) after and the 2nd liquid was measured. After measuring the number of micro organisms 6 hours after total test time, the capsule 6 hours after total test time was moved to new test fluid and the 2nd liquid, the trial was continued, and the number of micro organisms emitted into the test fluid 18 hours after a total was measured. These results were shown in Table 1. The capsule of the examples 3 and 4 after total 18-hour churning had become the suspended matter of flat and an indeterminate mold in digestive juices. As for one example of a comparison, and two examples of a comparison, the trace of a capsule did not remain, either. It became clear that it was the ideal sustained release capsule which this invention sustained release capsule has resistance also in pancreatin, and is gradually emitted in a small intestine from Table 1. In this example, although lactobacillus bifidus was chosen in the semantics representing a physiological active substance, lactobacillus bifidus is a life object and this is because it is very sharp for temperature, pH, and moisture. Therefore, if effectiveness is checked about lactobacillus bifidus, about the food and drugs as a physiological active substance which are other non-life objects, it can be predicted that it is naturally effective.
[0026] The sustained release capsule of different thickness like an example 4 was manufactured except having set thickness of the effect natural polysaccharide and the polyhydric-alcohol constituent of the thickness of example 7 natural polysaccharide and [an example 5 -] a polyhydric-alcohol constituent to 200 micrometers (example 5), 500 micrometers (example 6), and 800 micrometers (example 7). This capsule was shaken in the 1st liquid on the same conditions as examples 3 and 4 for 2 hours, and, subsequently it shook in the 2nd liquid for 16 hours. That is, at the time of experiment initiation, the 2-hour shaking back was measured in the 1st liquid, the dry weight of each capsule after 16-hour shaking was measured after 4-hour shaking and in the 2nd liquid in the 2nd liquid, and it was shown in the 2nd table. From the 2nd table, it became clear by adjusting the thickness of natural polysaccharide and a polyhydric-alcohol constituent that the emission time amount of capsule contents could be adjusted.
[0027]
[Table 2]

天然多糖類・多価アルコール組成物の膜厚	カプセルの重量（g）			
	実験開始	2時間後（第1液）	6時間後（第2液）	18時間後（第2液）
実施例5 （200μm）	0.82	0.53	0.07	−
実施例6 （500μm）	0.97	0.75	0.37	0.19
実施例7 （800μm）	1.12	1.01	0.58	0.36

[0028] The hydrophilic cellulose was mixed with the example 8 Homo-sapiens insulin (Wako Pure Chem make) as an extending agent, the capsule was filled up so that Homo sapiens insulin 25iu might be contained per capsule, and it covered with hardened oil, and natural polysaccharide and a polyhydric-alcohol constituent like the example 6, and the same trial as an example 6 was performed. The dry weight of one capsule after test termination with the 1st liquid was about 90% of the first weight, and the dry weight after 4-hour shaking with the 2nd liquid was about 40% of the first weight. The capsule after 16-hour shaking with the 2nd liquid had become the suspended matter of flat and an indeterminate mold.

[0029]

[Effect of the Invention] This invention can make a physiological active substance use for an organism effectively by being alike, preventing the decomposition and deactivation in the stomach more and making a physiological active substance emit gradually in the part from a small intestine to the large intestine.

[Translation done.]